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Migraine

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Abstract | Migraine is a common, chronic, disorder that is typically characterized by recurrent disabling attacks of headache and accompanying symptoms, including aura. The aetiology is multifactorial with rare monogenic variants. Depression, epilepsy, stroke and myocardial infarction are comorbid diseases. Spreading depolarization probably causes aura and possibly also triggers trigeminal sensory activation, the underlying mechanism for the headache. Despite earlier beliefs, vasodilation is only a secondary phenomenon and vasoconstriction is not essential for antimigraine efficacy. Management includes analgesics or NSAIDs for mild attacks, and, for moderate or severe attacks, triptans or $5HT_{1B/1D}$ receptor agonists. Because of cardiovascular safety concerns, unreliable efficacy and tolerability issues, use of ergots to abort attacks has nearly vanished in most countries. CGRP receptor antagonists (gepants) and lasmiditan, a selective $5HT1_F$ receptor agonist, have emerged as effective acute treatments. IntramuscularonabotulinumtoxinA may be helpful in chronic migraine (migraine on ≥15 days per month) and monoclonal antibodies targeting CGRP or its receptor, as well as two gepants, have proven effective and well tolerated for the preventive treatment of migraine. Several neuromodulation modalities have been approved for acute and/or preventive migraine treatment. The emergence of new treatment targets and therapies illustrates the bright future for migraine management.

Migraine is a common chronic, neurovascular brain disorder with major effects on patients and society[1–7]. Migraine affects ~15% of the general population globally[3,8] and is typically characterized by recurring, often highly disabling[9] attacks of severe headache, nausea, vomiting, super-sensitivity to light and sound, and other variable physical, mental and psychological signs and symptoms, lasting for 4–72 h (REF.[5]). Up to a third of patients may experience transient focal neurological aura symptoms in at least some of their attacks[5,8,10]. Generally, migraine attacks are multiphasic events with premonitory (sometimes also termed prodromal) symptoms 2–48 h prior to the attack[11–13] and postdromal symptoms for hours or days after the resolution of headache pain[14] (FIG. 1). In effect, migraine attacks may repeatedly incapacitate patients physically, mentally and socially for many days.

The presence, characteristics, severity, duration, frequency and associated features of migraine attacks show wide, partly sex-dependent, interindividual variability, and can also substantially vary within patients across a lifetime. In women, migraine attack frequency is influenced by fluctuations in sex hormone levels; attacks typically begin in puberty, frequently occur perimenstrually, temporarily disappear during pregnancy and while breastfeeding, and usually worsen and increase in frequency during menopause, often substantially decreasing in frequency or disappearing afterwards (for review see REFS[15,16]).

Migraine attacks and patients are diagnosed using the International Classification of Headache Disorders (ICHD) diagnostic criteria and defines patients with migraine as 'people ever having had at least two attacks of migraine with aura or at least five attacks of migraine without aura'. Most patients have episodic migraine, although some patients develop chronic migraine (the presence of ≥15 headache days per month, at least eight of which meet the criteria for migraine, or respond to a triptan or ergotamine derivative). Of note, although chronic migraine may persist for a long time, the term may be confusing as it actually denotes 'very high frequency migraine' rather than 'a disorder that persists for a long time', which is the usual connotation for the term chronic.

This Primer focuses on the clinical presentation, epidemiology, pathophysiology and management of migraine. In addition, the bright future of migraine therapy, featuring several new emerging acute and preventive migraine-specific medications, is highlighted.

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Epidemiology

Prevalence

The cumulative lifetime risk of ICHD-3-defined migraine in the general population is very high: ~33% in women and 18% in men[17]. The 1-year prevalence of migraine[5], that is the prevalence among individuals with ICDH-3-defined migraine who have had at least one attack in the previous year — known as 'active migraine prevalence' — is 8–15% worldwide, but is highly dependent on age, sex and migraine subtype[15] (FIG. 2).

Migraine attacks may begin at any age, typically in puberty and adolescence but only rarely after 50 years of age[3,4]. In one large study, the median age at onset was 23–25 years, with a peak between 15 and 19 years[17]. Until puberty, the prevalence of migraine is similar in boys and girls (~5%). In puberty, the prevalence of migraine rises, but more so in girls than in boys. Between 30 and 50 years of age the prevalence of migraine in women (30%) is three to four times higher than in men; after 50 years of age, the prevalence declines to ~5% in both men and women[18–20]. Precise incidence and lifetime prevalence figures are sometimes difficult to obtain because some people do not recognize early attacks and, particularly older people, forget they have had migraine attacks.

Attack frequency and duration

Among those with active migraine, the median monthly attack frequency is 1.5, a quarter have weekly attacks, and up to 5% have chronic migraine (see below)[3,8,21,22]. Accordingly, the total number of attacks experienced by an individual over a lifetime can vary considerably between individuals, from only a few to several thousand. The median duration of untreated migraine headache is one day, but can range from 4 h (2 h in children) to 3 days[3,21]. The duration of an entire attack is in fact longer if premonitory and postdromal symptoms are included (FIG. 1).

Chronic migraine

Most patients have the episodic form of migraine, with clearly defined attacks and attack-free periods. However, up to 5% of patients may develop chronic migraine[5] (BOX 1). Although a progressive increase of the attack frequency can occur spontaneously, it is often aggravated and/or induced by overuse of acute headache medications and/or caffeine[23]. Risk factors for migraine progression include high headache frequency, suboptimal acute migraine treatment, high headache-related disability, obesity, anxiety, allodynia and depression[22,24]. At the individual level, there may be dynamic transitions between chronic and high-frequency (that is, 10–14 monthly migraine days) episodic migraine[22].

Comorbidities

Migraine is often associated with comorbid conditions, which increase migraine-related disability and may interfere with its treatment.

Epilepsy. Migraine and epilepsy attacks share a paroxysmal presentation, various premonitory, ictal and postdromal features (such as headache, aura, cognitive and autonomic symptoms and sometimes coma) and a preventive response to valproate and topiramate, and may initiate each other or occur in close temporal relationship. In addition, migraine and epilepsy have a twofold to threefold increased, probably bidirectional, comorbidity, possibly due to shared genetic factors[15,25,26].

Depression and anxiety. Migraine and depression are common in the general population[27,28]. Overall, there seems to be a bidirectional relationship between migraine and depression; one analysis found genetic overlap for these disorders[29]. Indeed, in cohort studies, the risk of incident migraine in persons with existing major depression was threefold higher than in persons without depression, and incident major depression in persons with pre-existing migraine was more than fivefold higher than in persons without migraine history[27,28]. Moreover, patients with major depressive disorder and comorbid migraine have pronounced anxiety and physical symptoms[30]. Comorbid depression increases the risk of migraine chronification[30].

Stroke. Numerous clinic-based and population-based studies[31] and meta-analyses[32–34] have shown a link between migraine with aura and ischaemic stroke, primarily in women <50 years of age[33,35–38], but also in young men[39]. Increasing evidence suggests that the association of migraine with stroke may also extend to older age groups[40,41]. In women, the risk considerably increases if they smoke or use oral contraceptives[42,43]; the combination of both aggravating factors has a strong additive effect and is associated with the highest increase in risk[42,43]. However, migraine in itself is not a contraindication to the use of oral contraceptives as the absolute risk of stroke at young age still remains very low. Women with migraine who use oral contraceptives should refrain from smoking and should ideally use oral contraceptives with the lowest oestrogen content.

Although data are inconsistent, people with migraine may also have an 1.5-fold increased risk of haemorrhagic stroke[44]. In one large Danish 19-year cardiovascular follow-up study, the risks of ischaemic and haemorrhagic stroke in individuals with migraine were doubled[45].

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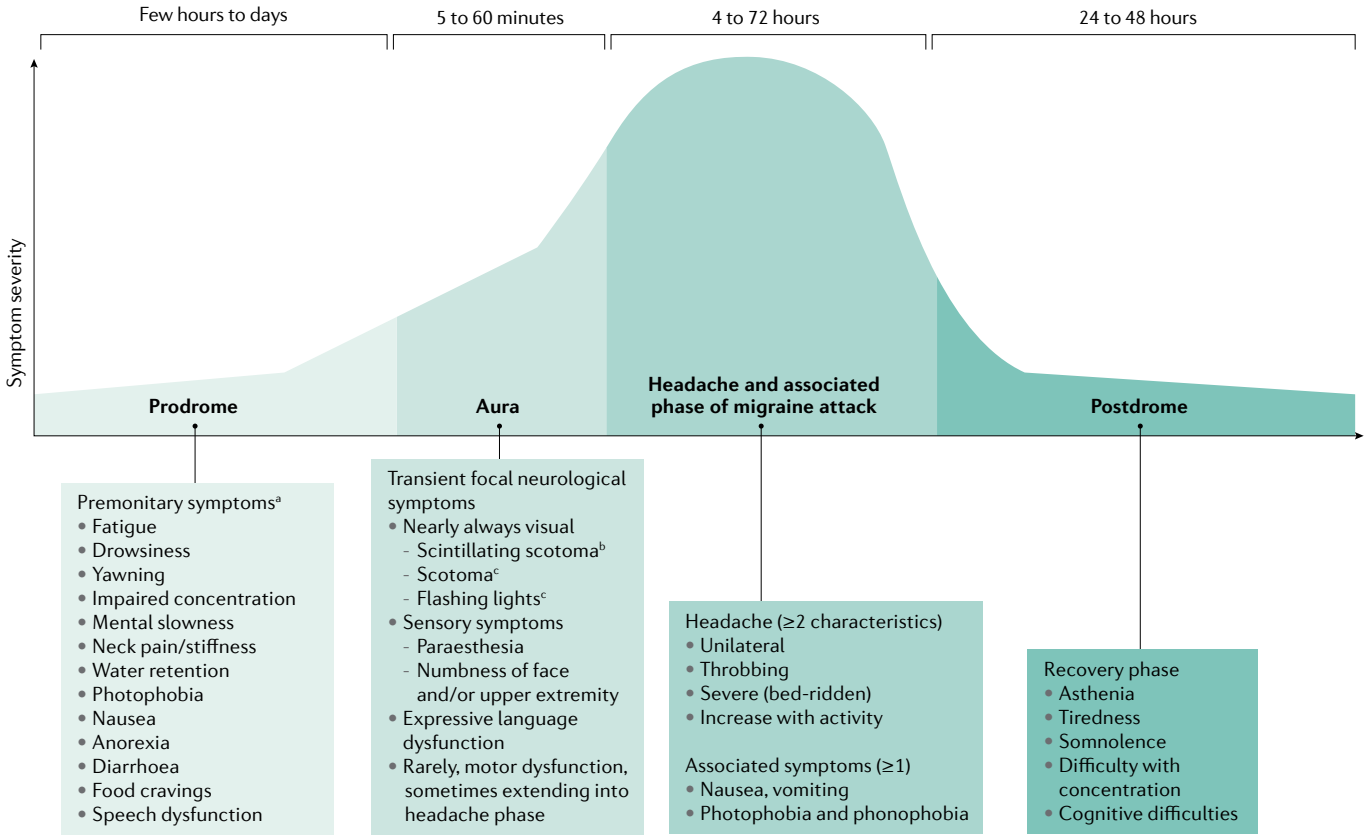

Fig. 1 | **Full-blown migraine attack.** An entire migraine attack may last up to 7 days including, in many patients, a prodromal phase, aura, headache and associated symptoms, and a postdromal phase. The prodromal phase with premonitory symptoms for several hours to days occurs in up to 80% of patients, whereas aura with transient focal neurological (mostly expanding visual) symptoms for up to an hour occurs in up to one-third of patients. By definition, the headache phase with associated symptoms lasts between 4 h (in children 2 h) and 3 days. The postdromal recovery phase can also last up to 2 days. [a]Occurring in one-third of patients. [b]Most common. [c]Less common.

The association was stronger in the year after migraine diagnosis, in women and in those with migraine with aura, and persisted after additional multivariable adjustments for body mass index and smoking status.

In addition to stroke, other cardiovascular events occur more frequently in those with migraine than in the general population. For example, most[46–50], but not all[51], brain imaging studies have linked migraine with clinically silent white matter or infarct-like lesions. This association is strongest for migraine with aura, particularly for stroke lesions. The association with white matter lesions may also extend to non-migraine headaches[48,52]. In addition, some studies have found an association between migraine with aura and patent foramen ovale (PFO)[53]. This association may be involved in the increased risk of stroke in patients with migraine[54].

Cerebral infarcts occurring in the course of, or immediately following, an attack of migraine with aura (known as migrainous infarction[5]) are rare. The underlying mechanism is unknown, but may be related to multiple severe spreading depolarizations (SDs; a slowly propagating (~3 mm/min) depolarization event within the brain tissue), vasoconstriction and in situ thrombosis[35]. A diagnosis of migrainous infarction should only be established after exclusion of other potential causes of cerebral ischaemia. Theoretically, the temporal relationship may also be reversed, that is, first cerebral ischaemia (for instance due to increased risk of atrial fibrillation)[55], which induces SD, which in turn triggers migraine aura and headache.

Myocardial infarction. There is increasing evidence of higher vascular risk profiles among patients with migraine[56]. Moreover, several population-based studies have found associations between migraine and myocardial infarction, coronary procedures and cardiovascular mortality[36,37,57–59]. In a meta-analysis, people with migraine had an increased risk of myocardial infarction (pooled adjusted effect estimate 1.33, 95% CI 1.08–1.64) and angina (pooled adjusted effect estimate 1.29, 95% CI 1.17–1.43) compared with people without migraine[60]. Risks are also increased in women in the postpartum phase[61], an often overlooked issue. In the Danish population-based 19-year cardiovascular follow-up study described above, risks of myocardial infarction and venous thromboembolism were increased by 50% and the risk of atrial arrhythmia was increased by ~25%[45]. Similar to stroke, the associations were independent of body mass index and smoking status, and were stronger in the year after migraine diagnosis, in those with migraine with aura and in women.

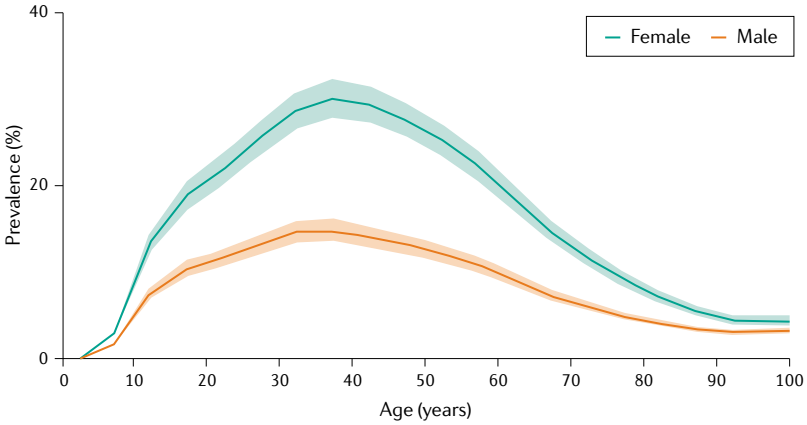

Fig. 2 | **One-year prevalence of migraine.** The 1-year (or active) prevalence in relation to age in people who fulfilled the lifetime prevalence criteria for migraine with aura (at least two attacks) or without aura (at least five attacks) and who had had at least one attack of migraine in the previous year. The 1-year prevalence steeply rises around puberty, continues to rise up to two or three times higher in women in the reproductive age range, and declines again after 45–50 years of age, notably in women. Peak prevalence of active migraine is ~40 years of age with 35% of women and 15% of men affected. Active migraine occurs in ~5% of young children and ~5% of the older people. Adapted from REF.[4], CC BY 4.0.

These data, combined with the stroke data above, strongly suggest that migraine is an important cardiovascular and cerebrovascular risk factor. Potential mechanisms for the increased risk in migraineurs of experiencing a stroke or myocardial infraction and for worsening of stroke outcome are discussed in BOX 2.

Other conditions. A consistent link has been found between restless legs syndrome and migraine[62] with odds ratios ranging from 1.22 (95% CI 1.14–1.30) in cohort studies to 4.19 (95% CI 3.07–5.71) in case–control studies[62]. Although no convincing evidence from clinical epidemiological studies has been obtained, attention deficit hyperactivity disorder and Tourette syndrome have been found to be genetically linked to migraine[29]. In addition, some reports suggest an increased risk of chronic pain disorders, such as irritable bowel syndrome, chronic fatigue syndrome, fibromyalgia, musculoskeletal pain and arthritis in patients with migraine[63,64]. Moreover, a large, 10-year longitudinal French study among primarily white non-obese women who were mostly teachers, found that self-reported active migraine was associated with a 30% lower relative risk of pharmacologically treated type 2 diabetes mellitus[65]. As the prevalence of active migraine declined in the years prior to the diabetes diagnosis, diabetes mellitus might even prevent migraine expression.

Mechanisms/pathophysiology

Although understanding migraine attack pathophysiology has substantially improved, the pathogenesis of the disease migraine (that is, why and how attacks are repeatedly triggered or occur spontaneously) remains poorly understood. Part of the challenge is in the unpredictable episodic nature of migraine, which complicates reliable data capture during spontaneous attacks, particularly in the early onset phase. To study the pathophysiology of migraine, attacks can be triggered by administration of certain substances[66] (BOX 3). These models have provided critically important insights into migraine mechanisms, but results from these studies must always be validated against those in spontaneous attacks. Likewise, results from animal models must be verified in human studies. Advances in genetics, neurophysiology, and structural and functional imaging, and pharmacological studies with migraine-specific treatments, have provided a clear but still incomplete roadmap for a better understanding of migraine pathophysiology.

Spreading depolarization and migraine aura

Aura symptoms commonly propagate slowly in a manner that reflects spread of the underlying phenomenon from a focal site of initiation along contiguous areas of brain cortex[67]. Positive symptoms of aura (such as scintillations and paraesthesia) often precede negative symptoms (such as scotoma and loss of sensation). Functional imaging studies with SPECT, PET and functional MRI (fMRI) during migraine aura have revealed propagated changes in blood flow from brief hyperperfusion followed by long-lasting hypoperfusion, in regions of the brain that are correlated with aura symptoms (for review see REF.[68]).

Several lines of clinical and experimental evidence strongly suggest that migraine aura is caused by SD, previously known as spreading depression (for review see REFS[69,70]). During SD, most if not all, cells in a brain area undergo near-complete membrane depolarization associated with massive efflux of K^+ and numerous neurotransmitters and neuromodulators including glutamate, influx of H_2O, Na^+ and Ca^{2+}, and neuronal swelling[70]. SD has profound effects on tissue metabolism and perfusion[71], second messenger activity, enzyme activity and gene expression. How SD spontaneously start and end is unknown. In one study of a genetic mouse model of migraine with aura, 'plumes' of glutamate release due to inefficient glutamate clearance preceded and probably initiated SD[72,73].

Although convincingly demonstrated in tissue and animal experiments, and in direct recordings of the human brain after cerebral trauma and ischaemia[70], SD has not yet been unequivocally observed during aura in humans. Most likely this is due to the logistic and technical challenges involved in capturing an SD non-invasively in an erratic paroxysmal disorder[70]. In one study using fMRI, the investigators scanned two exercise-induced auras in a single patient and three spontaneous auras in two other patients; the findings, although suggestive, did not unambiguously point to SD[74]. Another study of migraine aura induced by hypoxia, sham hypoxia or physical exercise found a reduced blood oxygen level-dependent (BOLD) response in patients reporting scotoma, and an increased BOLD response in patients who only experienced positive symptoms[75]. In addition, this study found that patients with visual symptoms in both eyes had changes in BOLD response in both brain hemispheres. The authors of this study suggested that the different aura symptoms reflected different forms of cerebral dysfunction that correspond to changes in BOLD signal reactivity.

Trigeminovascular activation and headache

The trigeminovascular pathway (for reviews see REFS[76,77] and FIG. 3) originates in trigeminal ganglion (TG) neurons and its projections to the dura mater are enriched for the neuropeptide calcitonin gene-related peptide (CGRP). Peripheral axons extend to the pia, dura and large cerebral arteries, and central axons extend to the trigeminocervical complex (TCC). Neurons in the dorsal horn of the TCC consist of high-threshold and wide-dynamic range neurons that receive further input from periorbital skin and pericranial muscles (FIG. 3). The ascending axonal projections of trigeminovascular TCC neurons convey monosynaptic nociceptive signals to brainstem, hypothalamic and thalamic neurons. These nuclei are involved in the regulation of a wide range of responses to pain, including sensory (pain), affective (anger, anxiety, fear and depression), autonomic (yawning, lacrimation and urination), endocrine (stress response) and behavioural (seeking a dark and quiet environment and falling asleep) responses[78,79]. Relay trigeminovascular thalamic neurons that project to the somatosensory, insular, motor, parietal association, retrosplenial, auditory, visual and olfactory cortices mediate the sensory discriminative components of migraine (such as pain intensity, location and quality) and the numerous cortically mediated symptoms of migraine (such as difficulty focusing, motor clumsiness, phonophobia, photophobia, transient amnesia, allodynia and osmophobia)[77,80].

Spreading depolarization as a putative trigger for trigeminovascular activation. Experimental data in animal models indicates that SD activates trigeminal nociceptive pathways[81–83] and, therefore, might be capable of triggering headache. SD is associated with activation of pial and dural macrophages and dendritic cells[84], closure of the glymphatic pathway[85], and release of a variety of potential nociceptive mediators via opening of neuronal pannexin 1 mega channels with activation of caspase 1 (REF.[86]). These events may then activate peripheral trigeminovascular neurons with cell bodies in the TG[82] and subsequently second-order trigeminovascular neurons in the spinal trigeminal nucleus and upper cervical spinal cord[81] (FIG. 4). As mentioned above, whether SD is a trigger for migraine attacks in humans has long been debated, without consensus[87,88]. Regardless, in animal models, SD is a relevant translational model for migraine. Numerous endogenous factors (such as gene variants and hormones) and exogenous factors (such as diet and drugs) that modulate migraine in humans also modulate the susceptibility of brain tissue to SD in animal models (see also below)[69,89–91].

The role of CGRP. The role of CGRP in migraine pathophysiology has been extensively reviewed elsewhere (see REF.[92]). TG stimulation results in CGRP and substance P release in cats and humans, CGRP is released into the superior sagittal sinus in rats, both of which are attenuated by antimigraine treatments[92]. Moreover, CGRP, but not substance P, is released into the cranial circulation of cats with superior sagittal sinus stimulation, which is blocked by a triptan ($5HT_{1B/1D}$ receptor agonist) but not a plasma protein extravasation inhibitor[93]. CGRP acts in the dura, TG, TCC, thalamus and periaqueductal grey (PAG) to mediate and modulate trigeminovascular nociceptive traffic. CGRP has been found to be released into the cranial circulation in patients with prolonged, severe migraine[94], and this release is attenuated by administration of triptans[95], predicting the successful proof-of-principle that CGRP blockade is effective in the treatment of migraine[96]. Comparable changes have been found in other studies, but could not be replicated in one major study, possibly because of important differences in controls and study designs[97]. In support of a role for CGRP in migraine pathophysiology, CGRP infusion may provoke migraine without aura attacks in migraineurs (but not in non-migraineurs)[6], calcitonin-like receptor and receptor activity-modifying protein 1 (which comprise the CGRP receptor) have been found in migraine-relevant brain structures such as TG, TCC and trigeminal afferents, and CGRP monoclonal antibodies prevent activation and sensitization of Aδ meningeal nociceptors (which are involved in migraine pathogenesis)[98] and HT trigeminovascular neurons in the TCC[99].

Clinical manifestations of peripheral and central sensitization. Over the course of an hours-long migraine attack, headache intensity increases and a variety of

Box 1 | **ICDH3 diagnostic criteria for migraine**[5]

Migraine without aura

At least five migraine attacks fulfilling the following three criteria, and that are not better accounted for by another International Classification of Headache Disorders third edition (ICHD-3) diagnosis.

- Headache attacks lasting 4–72 h (untreated).
- Headache has at least two of the following four characteristics: unilateral location, pulsating quality, moderate or severe pain intensity, aggravation by or causing avoidance of routine physical activity.
- During headache at least one of the following: nausea and/or vomiting, photophobia and phonophobia.

Migraine with aura

At least two attacks that fulfil the following two criteria and that are not better accounted for by another ICHD-3 diagnosis.

- One or more of the following fully reversible aura symptoms: visual, sensory, speech and/or language, motor, brainstem, retinal.
- At least three of the following six characteristics: at least one aura symptom spreads gradually over ≥5 min, two or more aura symptoms occur in succession, each individual aura symptom lasts 5–60 min, at least one aura symptom is unilateral, at least one aura symptom is positive, the aura is accompanied or followed within 60 min by headache.

Probable migraine

Attacks that fulfil all but one of the criteria for 'Migraine without aura' or 'Migraine with aura' that do not fulfil or are not better accounted for by another ICHD-3 diagnosis.

Chronic migraine

Headache (migraine-like or tension-type-like) that meets the following two criteria on ≥15 days/month for >3 months, and that is not better accounted for by another ICHD-3 diagnosis.

- Occurring in a patient who has had at least five attacks fulfilling criteria for 'Migraine without aura' or at least two attacks fulfilling criteria for 'Migraine with aura'.
- Headache occurring on ≥8 days/month for >3 months, fulfilling any of the following: criteria for 'Migraine without aura', criteria for 'Migraine with aura' or that is believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative.

Box 2 | **Putative mechanisms for stroke and myocardial infarction in migraine**

Ischaemic stroke

Spreading depolarization (SD) events may also occur in the setting of stroke and brain injury[159,255]. Although SD is not believed to be injurious in healthy cortex, it may worsen injury in ischaemic tissue[159,255]. SD also has profound effects on cerebral vasculature, including long-lasting vasoconstriction and blood–brain barrier disruption[71]. In experimental stroke, peri-infarct SD occurred more frequently in familial hemiplegic migraine type 1 (FHM1) mice and occurred sooner than in wild-type mice, increasing the metabolic supply–demand mismatch and susceptibility to ischaemia[159]. Accordingly, the viability threshold for ischaemic cerebral blood flow was raised, and infarction occurred earlier, was more extensive and was associated with a higher mortality[159]. The effect on infarct size was greater in female than in male mutant mice (in line with the higher risk of stroke in women with migraine) and in S218L than in R192Q mice (consistent with the greater dysfunction of $Ca_V2.1$ channels and more severe phenotype than in S218L mice). The NMDA glutamate receptor antagonist MK-801 limited infarct size and improved both tissue and clinical outcome. Interestingly, Leaner mice, unlike FHM1 mice, have a loss-of-function mutation in *Cacna1a* and displayed smaller infarcts than controls[15]. Altogether, SD may explain, at least in part, the increased risk of ischaemic stroke in migraine with aura[15,35]. Patients who are more susceptible to SD (such as those with frequent or severe migraine auras) appear to be more susceptible to cerebral ischaemia[36,159].

Another potential risk factor for stroke in migraine involves patent foramen ovale. Multiple studies have indicated an association between migraine, specifically migraine with aura, and patent foramen ovale[53]. While it is often assumed that stroke in those with migraine with aura is due to migrainous infarction (stroke occurring as the result of migraine mechanisms), it is in fact rare for stroke to occur in the setting of a migraine attack. Conversely, cryptogenic stroke (stroke with no identifiable cause), is associated with both patent foramen ovale and migraine with aura[54]. Accordingly, the increased risk of stroke in those with migraine with aura could possibly be related to patent foramen ovale as a common risk factor. This could explain the observations that stroke risk in migraine is particularly increased in younger individuals and those with causes of hypercoagulability, such as smoking and the use of oral contraceptives containing high-dose oestrogen, which increase the risk of embolism through a patent foramen ovale.

Myocardial infarction

An extensive study integrating multiple state-of-the-art biological approaches was the first to show that the G allele of the non-coding DNA variant rs9349379 in the *PHACTR* locus on 6p24 raises the risk of myocardial infarction and reduces the risk of migraine, cervical artery dissection, fibromuscular dysplasia and hypertension[256]. Migraine increases the risk of myocardial infarction and cervical artery dissection[257,258]. The variant was shown to increase *EDN1* (encoding vascular endothelin 1) expression, raising the levels of endothelin 1, a potent vasoconstrictor and atherosclerosis promoter. Whether this variant is involved in promoting myocardial infarction in migraine requires further investigation.

associated sensory symptoms appear. This within-attack progression is believed to reflect enhanced excitability and responsivity (collectively termed sensitization) of peripheral and central trigeminovascular neurons. Sensitization of meningeal nociceptors, which probably occurs as a result of their continuous exposure to algogenic pro-inflammatory molecules (such as CGRP, nitric oxide and PGE_2) that are capable of altering their membrane resting potential, become spontaneously active and begin to respond to mechanical stimulation of the dura to which they normally show minimal or no response[100] (FIG. 4). Sensitization of central trigeminovascular neurons in laminae I and V of the TCC, thalamic posterior and ventral posteromedial nuclei neurons (FIG. 4) leads to increases in spontaneous activity, receptive field expansion, and response to innocuous stimulation of cephalic and extracephalic skin areas and muscle stretching[101]. Clinical manifestations of these processes, which typically develop during the migraine attack and often outlast its termination by 2–3 days, could include (1) transient intensification of headache during activities that increase intracranial pressure, such as bending over or coughing (peripheral sensitization); (2) cephalic allodynia with scalp and muscle tenderness and hypersensitivity to touch, often described by patients as avoiding earrings, glasses, hats, or any other items that contact the facial skin[102] (TCC sensitization); and (3) extracephalic allodynia often causing patients to remove tight clothing and jewellery, and to avoid being touched[103] (thalamic sensitization). People with a high frequency of migraine attacks, such as those with chronic migraine, may consequently show permanent hypersensitization.

The role of the brainstem and diencephalon

Subcortical structures are well placed to play a role in migraine given the diffuse and diverse nature of migraine symptoms from pain through sensory sensitivity to cognitive dysfunction. Indeed, a role of subcortical structures in migraine is supported by data from human imaging studies, and there is a good basic science rationale to link these structures to the pathophysiology of migraine (for review see REFS[77,104]).

Human studies. During the premonitory phase of migraine, prior to the onset of headache and aura, functional imaging studies have shown activations in the region of the hypothalamus, PAG and dorsolateral pons[79,105]. These findings raise the possibility that migraine begins in those structures, and that nociceptive signalling is not required for the initiation of a migraine attack. However, this concept is complicated by studies showing that hypothalamic activation before attack onset might happen in the absence of premonitory symptoms[106]. Nausea involves activation of the medulla in the premonitory phase. Activation of the dorsolateral pons occurs during the pain phase[107], which is lateralized in unilateral headache. This pattern is very distinct from that in the trigeminal autonomic cephalalgias[108], in which activation of a more posterior hypothalamic region is seen[109].

Animal studies. Although many animal studies evaluating the pathophysiology of migraine have been carried out, only key results are discussed here; for an extensive review of the literature, see REF.[110]. Activation of trigeminal neurons with durovascular inputs can be achieved by chemical or electrical means and each has advantages and drawbacks. Administration of the $Ca_V2.1$ (P/Q type) voltage-gated calcium channel blocker ω-agatoxin IVA into the PAG can facilitate trigeminocervical durovascular nociceptive traffic[111]. Local PAG injections of acutely effective antimigraine agents[112] inhibit TCC activation. Dopamine has a role in yawning, a prominent premonitory symptom in migraine[11]. The TCC has dopamine receptors that are inhibitory when activated[113]. The posterior hypothalamic nucleus A11 is an important source of descending dopaminergic input to the dorsal horn; activation of A11 inhibits TCC nociceptive traffic and lesioning facilitates that traffic, which can be reversed by administration of a triptan[114].

The role of intracranial blood vessels

An intimate role for blood vessels in migraine pathophysiology is not surprising given that the brain itself is devoid of nociceptive innervation, and that intracranial pain perception is largely limited to the meninges and large cerebral arteries. Moreover, a marked long-lasting reduction of cerebral blood flow has been observed in the aftermath of migraine attacks, particularly after migraine with aura[115]. Finally, only vasodilating substances have thus far been shown to provoke migraine-like attacks in migraineurs[66].

Whether migraine headache is caused by cerebral, meningeal or extracranial vasodilation is debated[116,117]. In human magnetic resonance angiography studies, placebo-controlled nitric oxide-provoked[118] and spontaneous[119] migraine attacks were not associated with meningeal or extracranial vasodilation. However, attacks induced by CGRP, cilostazol or sildenafil were associated with ictal dilation of the middle meningeal artery[120,121]. Of note, middle cerebral arterial dilation during spontaneous attacks persisted after relief with sumatriptan, whereas extracranial arteries constricted[119]. These data, together with the clinical efficacy of non-vasoconstrictor gepants in migraine (see below), suggest that (1) cerebral arterial dilation is an epiphenomenon reflecting activation of perivascular afferents in response to vasodilatory neurotransmitters such as CGRP; (2) the acute antimigraine effects of sumatriptan and gepants are mediated, either by a selective but non-vasoconstrictor effect on extracranial arteries, or by a non-vascular neuronal effect; and (3) various signalling molecules (such as CGRP and pituitary adenylate cyclase-activating peptide) initiate a cascade of intracellular processes that result in opening of ATP-sensitive potassium channels on vascular smooth muscle cells within the intracranial arteries. Efflux of potassium causes hyperpolarization and vasodilation of these arteries, and an increase in extracellular potassium leading to sensitization of perivascular trigeminal primary afferents in the walls of intracranial arteries. Nociceptive impulses from these arteries are then transmitted to and processed by cortical and subcortical regions via ascending trigeminal pain pathways, ultimately resulting in the perception of migraine pain[6].

The interictal migraine brain state

Between migraine attacks, the brain of migraineurs exhibits structural and functional differences compared with the brain of healthy controls (for review see REF.[122]). Altered morphologies include decreased grey matter volume in pain-processing areas (such as the anterior cingulate cortex, insula, frontal lobe, parietal lobe, basal ganglia and cerebellum), increased grey matter volume in the somatosensory cortex, increased white matter lesions[46–50], and decreased white matter integrity. These structural abnormalities might be driven by recurrent ischaemia and/or nociceptive overload of brain areas that process pain, or might be just a consequence of repeated migraine attacks.

Functional interictal alterations include enhanced visual, auditory, somatosensory and motor-evoked responses, enhanced nociceptive processing, and abnormal pain processing in the rostral pons. Such functional alterations offer an explanation for why the migraine brain undergoes dysfunctional habituation of sensory processing and why it exhibits reduced ability to modulate pain[77]. Moreover, interictal levels of glutamate are increased in the visual cortex of migraineurs without aura, directly supporting the hypothesis of cortical hyperexcitability and, consequently, increased susceptibility for SD in migraine[123]. Collectively, these structural and functional abnormalities are likely to play a role in cortical hyperexcitability of the migraine brain. Determining whether these structural and functional abnormalities are a result or a cause of the repetitive migraine attacks is critical to improving understanding of migraine pathophysiology.

The genetic basis of migraine

Clinical expression of migraine is 40–60% determined by genetic factors[15,124,125] and for the remainder by non-genetic endogenous (such as age and sex hormone fluctuations) and exogenous (such as head trauma, fatigue and sleep changes) risk-modulating and trigger factors[15]. Genome-wide association studies (GWAS) have identified 38 susceptibility loci for migraine[126]. Of note, none of the gene variants previously identified in hypothesis-driven candidate gene association studies had a significant signal in the GWAS; this observation underlines the risk of false-positive findings in small studies testing gene variants selected owing to a putative role in migraine pathophysiology[127].

In a large Finnish study[128], common migraine-associated variant load measured via the polygenic risk score (PRS) was increased in familial migraine compared with non-familial migraine (OR 1.76). The increase was most pronounced in familial hemiplegic migraine (FHM; OR 1.96), followed by migraine with typical aura (OR 1.85) and migraine without aura (OR 1.57). Patients with a young age at migraine onset, the highest migraine

Box 3 | Experimental provocation of migraine without aura attacks

Systematic analysis of the effects of naturally occurring signalling molecules has provided important data on migraine mechanisms and potential therapeutic targets[66]. The nitric oxide donor glyceryl trinitrate (GTN) is the most extensively studied[259]. Typically, GTN infusion induces attacks of migraine without aura (often with premonitory symptoms) in up to 83% of patients with migraine without aura, in 67% of those with migraine with aura and in 30% of patients of those with hemiplegic migraine[108]. Attacks are not provoked in controls who do not have migraine and GTN does not induce aura. As sildenafil, a selective inhibitor of cGMP-hydrolysing PDE_5, induces migraine attacks in 77% of patients, upregulation of cGMP seems important in migraine pathophysiology[260]. A similar migraine provocation pattern as with GTN has been seen with CGRP[261]. Pituitary adenylate cyclase-activating polypeptide-38 (PACAP-38) induces migraine attacks in ~70% of patients[262,263]. Adenylate cyclase is activated via transmembrane receptors, and intracellular cyclic AMP in vascular smooth muscle cells of cerebral arteries is increased by CGRP and PACAP-38 (REFS[22,63]). Cilostazol is a selective inhibitor of phosphodiesterase type 3, inhibiting breakdown of cAMP and causing cAMP accumulation via an intracellular pathway; the substance triggers migraine attacks in 86% of patients[264].

Altogether, two key pathways seem important for migraine initiation: cGMP and cAMP intracellular signalling. Upregulation of second messenger molecules lead to opening of ATP-sensitive potassium channels (K_{ATP}) and large (big)-conductance calcium-activated K^+ (BK_{Ca}) channels that are expressed in migraine-relevant structures[265]. Indeed, levcromakalim (a K_{ATP} channel opener) and MaxiPost (a BK_{Ca} channel opener) induced migraine attacks in 95–100% of patients with a history of migraine[265]. K_{ATP} channel and BK_{Ca} channel blockers might be potential targets for novel antimigraine drugs[6,266].

severity and higher numbers of ICHD-3 migraine symptoms had the highest PRS[5]. The explained variance, however, was still disappointingly low, most likely due to the limited number of risk loci used for this analysis[126] and their small individual effect sizes (2.9–8.2%)[129].

The Finnish study[128] and other studies[15] also provide strong genetic support for the view that FHM, migraine with aura and migraine without aura are part of a clinical and genetic migraine spectrum[15,124].

Mechanistic and diagnostic interpretation of GWAS-identified migraine loci. Translating GWAS findings to disease pathways is complicated by the large number of variants that confer susceptibility to migraine and their small effect sizes. Preliminary research suggests that migraine risk loci are involved in glutamatergic neurotransmission, synapse development, synaptic plasticity, metalloproteinases, metabolism and pain sensing[15,126,128]. Gene interaction network analyses might further reveal how these genes work in concert by highlighting relevant disease pathways, and neuronally differentiated human induced pluripotent stem cells with these mutations may further help to identify the molecular and cellular effects of these mutations.

Monogenic migraine syndromes

Migraine occurs in four rare Mendelian syndromes: cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations (RVCL-S), familial advanced sleep phase syndrome (FASPS) and FHM[15]. Studying these subtypes of migraine might be useful in improving our understanding of the pathophysiology of migraine.

CADASIL is caused by mutations in *NOTCH3*. *NOTCH3* encodes a protein that has a crucial role in survival and function of vascular smooth muscle cells and maintenance of small blood vessels, including cerebral vessels[130]. Migraine occurs in more than one-third of patients with CADASIL, and frequently precedes other symptoms by a decade[131]. RVCL-S is a progressive cerebral and systemic small-vessel disease, caused by carboxy terminal truncating mutations in *TREX1*, which encodes a 3′–5′ exonuclease[132,133]. Migraine is a striking feature in certain families with RVCL-S[132–135]. FASPS is a sleep disorder caused by missense mutations in *CSNK1D*, which encodes casein kinase 1δ, a regulator of circadian rhythms[136]. Migraine with aura co-segregated with the pathogenic mutation in two

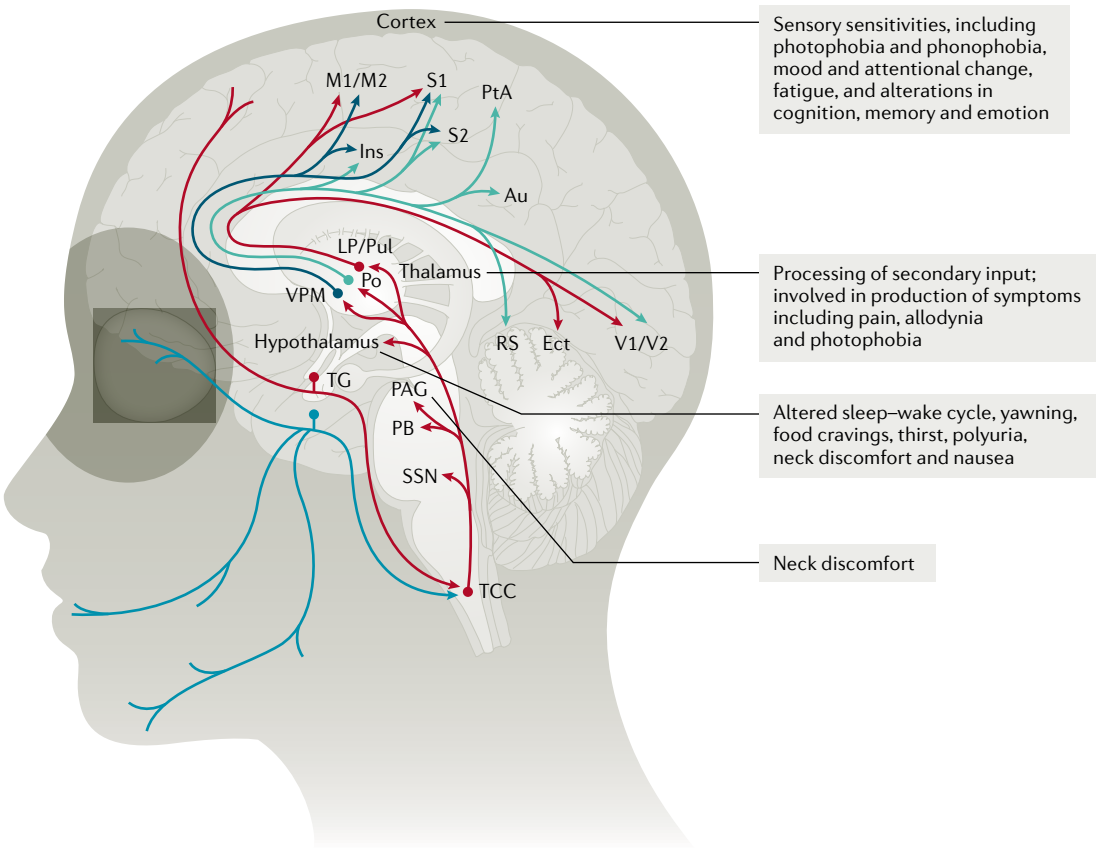

Fig. 3 | **Anatomical substrates of migraine.** The trigeminovascular pathway provides the anatomical and physiological substrate for migraine headache. Au, auditory cortex; Ect, ectorhinal cortex; Ins, insular cortex; LP, lateral posterior thalamic nucleus; M1, primary motor cortex; M2, secondary motor cortex; PAG, periaqueductal grey; PB, parabrachial nucleus; PtA, parietal association cortex; Pul, pulvinar; RS, retrosplenial cortex; S1, primary somatosensory cortex; S2, secondary somatosensory cortex; SSN, superior salivatory nucleus; TCC, trigeminocervical complex; TG, trigeminal ganglion; V1, primary visual cortex; V2, secondary visual cortex; VPM, ventral posteromedial nucleus. Adapted with permission from REF.[254], The Journal of Neuroscience, and from REF.[13], Springer Nature Limited.

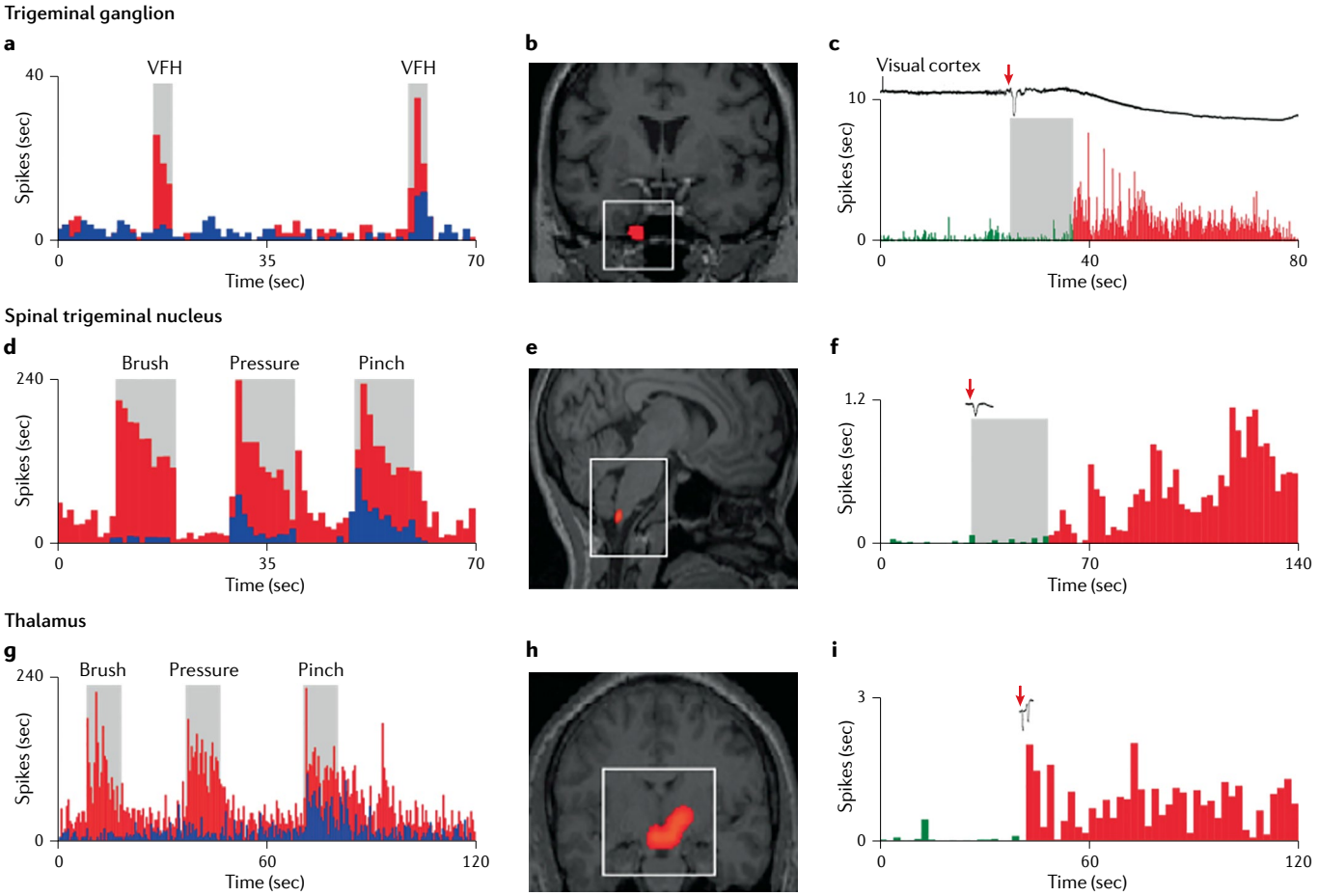

Fig. 4 | **Sensitization of neural circuits mediating the headache phase of migraine.** The trigeminal ganglion (panels **a**–**c**), spinal trigeminal nucleus (panels **d**–**f**) and thalamus (panels **g**–**i**) are involved in migraine pathophysiology. Sensitization of meningeal nociceptors (panel **a**) and central trigeminovascular neuron in the spinal trigeminal nucleus (panel **d**) and posterior thalamus (panel **g**) by topical application of inflammatory mediators to the dura. Functional MRI (fMRI) images show sensitization of neurons in the trigeminal ganglion (panel **b**), spinal trigeminal nucleus (panel **e**) and posterior thalamus (panel **h**) during migraine. Activation of peripheral and central trigeminovascular neurons by cortical spreading depression is shown in panels **c**, **f** and **i** (delayed activation in panels **c** and **f**, immediate activation in panel **i**). VFH, von Frey hairs. Adapted with permission from REF.[254], The Journal of Neuroscience.

independent extended families[137]. Transgenic mouse models that overexpress CADASIL and FASPS causative mutations revealed, among other features, enhanced susceptibility to SD[136,137].

Hemiplegic migraine. In FHM and sporadic hemiplegic migraine (SHM), attacks of migraine with aura are associated with transient hemiparesis[5], although other aura and migraine symptoms are identical to those seen in non-hemiplegic migraine with aura[138]. Moreover, the headache and associated symptoms of hemiplegic attacks can be provoked by similar factors and treated with largely the same medications as non-hemiplegic migraine[15,138–140]. Other features that overlap in hemiplegic and non-hemiplegic migraine are female preponderance and increased prevalence of common migraine among first-degree relatives[15,138]. In most patients with FHM and SHM, hemiplegic and non-hemiplegic attacks alternate[15,138,139]. Altogether, although not identical to non-hemiplegic migraine, hemiplegic migraine is considered by most as a valid model to explore potential mechanisms involved in migraine pathophysiology[15].

Three FHM genes have been identified that encode proteins involved in controlling synaptic activity[15,139] (FIG. 5). FHM type 1 (FHM1) is caused by specific missense mutations in *CACNA1A*, which encodes the α_{1A} subunit of neuronal voltage-gated $Ca_V2.1$ calcium channels. These calcium channels control the release of neurotransmitters at peripheral and central synapses[141]. Clinical severity associated with FHM1 mutations varies considerably and is particularly severe with the S218L missense mutation that can also result in fatal attacks of severe cerebral oedema, seizures and coma triggered by trivial head trauma[142,143]. FHM2 is caused by missense mutations in *ATP1A2*, which encodes the α2 subunit of Na^+/K^+-ATPase pumps that facilitate neurotransmitter reuptake at synaptic clefts by glial cells in adults[142,143]. FHM3 is caused by missense mutations in *SCN1A*, which encodes the α1 subunit of neuronal voltage-gated $Na_V1.1$ sodium channels that are essential for generation and propagation of action potentials[144].

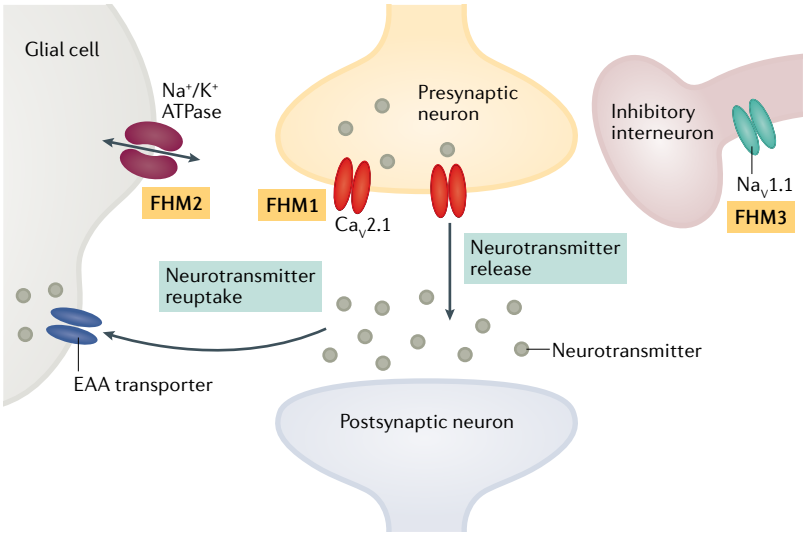

Fig. 5 | **Pathogenesis of familial hemiplegic migraine.** Familial hemiplegic migraine (FHM) 1–3 is caused by pathogenetic variants *CACNA1A* (encoding presynaptic $Ca_V2.1$ calcium channels), *ATP1A2* (encoding an Na^+/K^+-ATPase) and *SCN1A* (encoding $Na_V1.1$ sodium channels), respectively. Gain-of-function mutations in *CACNA1A* lead to increased calcium influx and increased glutamate release in synaptic clefts. Loss-of-function mutations in *ATP1A2* reduce glutamate reuptake and, therefore, increase glutamate levels, in synaptic clefts. Loss-of-function mutations in *SCN1A* cause reduced inhibitory activity, increased excitatory activity and increased glutamate release. EAA, excitatory amino acid.

Studies in cellular models expressing FHM causative mutations have revealed gain-of-function effects of neuronal $Ca_V2.1$ channels on excitatory glutamatergic neurons in FHM1, loss of glial Na^+/K^+ ATPase function in FHM2, and loss-of-function or gain-of-function effects for $Na_V1.1$ sodium channels on inhibitory GABAergic interneurons in FHM3 (REFS[145–147]). These findings suggest increased glutamate and potassium ion levels in the synaptic cleft enhancing susceptibility to SD as a final common pathway in all three FHM genotypes for hemiplegia and other aura symptoms[15,139]. Indeed, transgenic knock-in mouse models expressing human pathogenetic FHM1 and FHM2 missense mutations showed increased cortical glutamatergic neurotransmission leading to increased susceptibility to cortical SD[148–155]. Moreover, 'plumes' of glutamate release owing to inefficient glutamate clearance preceded and probably initiated SD in a FHM2 model[72,73].

FHM1 mouse models also displayed migraine-associated features, lending further support to their clinical validity. These features included hemiparesis[151,153], photophobia[156], cranial hyperalgesia interpreted as head pain[156,157], enhanced response to experimental jet-lag[158] (a known trigger for migraine attacks) and increased vulnerability to ischaemic stroke[159]. Similar to the findings in patients, the intensity of these effects and features was more pronounced in mice with the clinically more severe S218L mutation compared with the R192Q mutation, and depended on the levels of sex hormones, as the intensity was greater in female mice[151,152]. Moreover, FHM1 mice with the S218L mutation also had cerebellar ataxia, enhanced susceptibility to seizures, and delayed cerebral oedema after minor head trauma[149,160].

Several studies have failed to identify additional genes for FHM. In a large Dutch study, patients with hemiplegic migraine without a mutation in *CACNA1A*, *ATP1A2* or *SCN1A* had a mild phenotype more similar to that of common non-hemiplegic migraine[161]. Whole-exome sequencing in this study and a large Finnish[128,162] study failed to identify pathogenetic mutations in new genes. *PRRT2* has been suggested as a possible fourth hemiplegic migraine gene[163], but the relation with migraine is unclear as most carriers of *PRRT2* mutations have a movement disorder, not migraine[164], and neither the Dutch[161] nor the Finnish[165] whole-exome sequencing study identified any FHM-associated pathogenetic mutations in *PRRT2* in over 500 patients and families with FHM.

Initiation of migraine

Patient-reported triggers. Many people are convinced that attacks might be provoked by an extensive list of triggers; however, clear evidence is lacking. Provocation and observational studies were biased and had methodological issues[166–168]. Putative triggers might in fact be part of the premonitory symptom complex[13,77,166–168]; for instance, patients frequently feel stressed or irritated before attacks, or crave and eat certain foods (such as chocolate). These patients are then convinced that stress or chocolate has triggered the attack, rather than being a consequence of an already initiated attack. Thus, disentangling true triggers and premonitory symptoms is difficult.

The migraine attack triggering threshold. How naturally occurring migraine attacks are initiated is unknown. A plausible hypothesis[15] is that initiation of migraine attacks is caused by a complex interaction among: (1) a genetically determined lowered triggering threshold, (2) fluctuating migraine trigger threshold susceptibility-modulating factors (MTTSMF) such as oestrogen, that may temporarily further lower the triggering threshold, and (3) multiple patient-specific (external) trigger factors co-occurring when the triggering threshold is accidentally low.

Proving such a concept for natural triggers for migraine attacks is challenging. Most progress has been achieved by studying the effects of signalling molecules in experimental provocation studies (BOX 3). Indirect support for this hypothesis comes from the observation that CGRP, PACAP38 and VIP administration provokes attacks of cluster headache only in patients with chronic cluster headache (that is, without attack-free periods) or who are in an active bout of episodic cluster headache, but not in patients with episodic cluster headache who are in an inactive remission phase[169,170].

Phenotype modulation by sex hormones. Fluctuations in sex hormone levels are among the best candidates for MTTSMF (for review see REFS[15,16]). However, although supporting evidence has been obtained from a wide range of (pre)clinical observations, the evidence is still circumstantial. As previously mentioned, active migraine fluctuates based on hormonal changes throughout life. Moreover, migraine prevalence is higher in people with obesity, possibly due to increased conversion from testosterone into oestrogen in adipocytes, and exogenous hormone therapy such as oral contraceptives and other hormone replacement/supplementation

therapy may influence attack frequency and clinical features (for a review see REFS[15,16]). Further evidence supporting a link between migraine and hormone levels is that men with migraine have higher oestrogen levels than men without migraine[16]. In addition, menstrual cycle-related changes in oestrogen levels influence the activity of the trigeminovascular system, and sex-related differences and manipulation of sex hormone levels modulates the functional effects of *CACNA1A* mutations in transgenic mouse models[15]. In these mice, susceptibility to cortical SD was reduced, and velocity and frequency were increased in female mice compared with male mice, and these effects were partially revoked by ovariectomy and enhanced by orchiectomy[151,152,171]. The enhancing effects of FHM1 mutations on cortical SD susceptibility was thus reinforced by female gonadal hormones, probably by increasing cortical hyperexcitability, while male hormones reduced the excitability. Of note, modulation of cortical SD susceptibility occurred only in mutated mice and not in wild-type mice; however, another study using different methods of SD induction found a reduced threshold in wild-type mice[172].

Stress. Stress, or relief after a period of stress[173], are commonly reported as putative migraine trigger factors[174]. Stressful life events may also be risk factors for migraine progression[175]. However, the extent to which stress is a true trigger of migraine or is a premonitory symptom has been questioned[176]. Activation of hypothalamic and amygdala circuits may underlie premonitory mood disturbance and perception of stress and anxiety[177]. Conversely, stress is associated with plasticity in prefrontal, hippocampal and amygdala circuits putatively leading to migraine chronification[178], and might result in dynorphin release and activation of κ-opioid receptors in subcortical regions believed to be involved in migraine pathogenesis[179,180].

Diagnosis, screening and prevention

Diagnostic criteria

Migraine with or without aura. The diagnostic criteria of the International Headache Society define subtypes of migraine attacks[5] (BOX 1). To qualify as a patient with the disease migraine, individuals must have experienced at least two attacks of migraine with aura or five attacks of migraine without aura over their life[5]. The clinical features of migraine attacks vary substantially between patients, between attacks in the same patient, and over the patient's life. Although some researchers have suggested that migraine with aura and migraine without aura might be distinct disorders[20], most would agree that they are clinically and pathophysiologically more alike than different[15,181]. Of note, migraine diagnosis in children might be challenging because of a more difficult and primarily indirect history via the parents, more atypical features, greater prominence of gastrointestinal symptoms, and often shorter attack duration (2 h) compared with adults[5] (BOX 4).

Migraine aura. Migraine aura may precede or, rarely, accompany or even follow the headache in a migraine attack. Visual symptoms are the most common, but sensory, language, motor and 'brainstem' symptoms may also occur[182]. Aura symptoms typically spread and expand gradually over 30–60 min and, if more than one symptom is present, mostly occur in succession with visual symptoms usually occurring first[68,182]. The classic visual aura, a scintillating scotoma, starts with a perception of shimmering lights that expands like a wavefront, followed by impaired vision[183]. Scotoma without scintillation and stationary visual symptoms like flashing lights can also occur. These heterogeneous visual aura symptoms are probably a reflection of the different areas of visual cortex affected by the underlying physiological disturbance[68]. The most common sensory symptoms of aura include paraesthesia and numbness of the face and/or upper extremity, whereas language symptoms typically manifest with expressive language dysfunction[5].

Migraine with brainstem aura (previously referred to as basilar migraine) is a rare subtype of migraine with aura and includes symptoms such as dysarthria (difficulty with speech), vertigo, tinnitus, hyperacusis (reduced tolerance to noise), diplopia (double vision), ataxia and reduced consciousness[7]. Refined diagnostic criteria for migraine with brainstem aura were proposed in 2019 (REF.[184]). As previously mentioned, hemiplegic migraine is a rare, typically autosomal dominant, severe subtype of migraine with aura, associated with hemiparesis and other features of focal and global cerebral dysfunction, sometimes even including sterile meningoencephalitis and coma[5] (for review see REF.[15]).

Diagnostic work-up

Migraine is a clinical diagnosis based on patient-reported symptoms that are obtained by clinicians during a patient interview. Epidemiological research often uses questionnaires that elicit information from individuals necessary for the diagnosis. Diagnosis is based on criteria in the ICHD-3 (REF.[5]). As no objective disease-specific tissue or imaging biomarkers for migraine are available, an obligatory criterion for all primary headache disorders is that the diagnostic features are not attributable to another cause. An index of suspicion of a secondary cause that may mimic the headache and associated symptoms of migraine requires identification of red flags in the patient's history on physical or neurological examination that raise concern. Non-validated

Box 4 | Children and adolescents

Migraine occurs in 6% of children[267]. Although migraine prevalence in boys and girls is similar before puberty, in girls prevalence rises after menarche. Broadly speaking, the phenotype of migraine in children and adolescents is very similar to that in adults, although paediatric migraine can be less feature-full than the adult migraine. Attacks in children may sometimes be shorter than attacks in adults[5], The range of premonitory symptoms are the same in paediatric and adult migraine[268], and children can also have migraine aura and cranial autonomic symptoms[269]. Treatment is similar in children and adults[270,271], although many medicines routinely used have not been expressly studied in paediatric cohorts. Of note, there is some evidence that infantile colic is a precursor to migraine[272].

guides to eliciting historical and examination red flags have been published and are used by many clinicians in practice[185,186]. Diagnostic testing mostly consists of blood tests and imaging depending on the suspected differential diagnosis based on red flags or worrisome features that are identified during the patient's history or examination.

Differential diagnosis

Migraine can usually be readily distinguished from other primary headache disorders[5]; however, distinguishing attacks of probable migraine, chronic migraine or tension-type headache can be challenging[5]. Tension-type headaches are common, poorly defined, 'featureless' headaches that often coexist with migraine.

Distinguishing migraine from secondary headaches may be challenging, particularly when the headache has had a recent onset. Careful history and examination are required to identify secondary headaches. Sudden onset of headache or associated neurological symptoms, new headaches in individuals >55 years of age, associated fever and systemic illness are among the red flags that should raise concern for secondary headache[186].

Migraine aura may sometimes mimic transient ischaemic attacks[35] or epilepsy, in particular when occurring in the absence of headache (migraine aura without headache)[5]. Distinguishing features of migraine aura include the more gradual onset, slow (over minutes) progression, sometimes succession of the symptoms, complete reversibility (typically within 1 hour), and occurrence of positive visual symptoms and paraesthesia[187].

Screening

Screening for modifiable risk factors for developing the disease migraine is not possible, except perhaps that people after head trauma are at increased risk. Identifying risk factors for disease progression may provide opportunities to initiate preventive measures to reduce the burden of illness and prevent chronification.

Although some risk factors of migraine have been identified, there is no evidence that treating these risk factors alleviates migraine risk. For example, there is no evidence that weight loss might prevent migraine or its progression in people with obesity, and there is no evidence that treating depression or anxiety mitigates migraine disease progression. Medication overuse is probably the sole risk factor for migraine progression for which prevention or stopping has been shown to prevent or mitigate migraine progression.

Management

Migraine management may include various combinations of pharmacological therapies, neuromodulation, and behavioural acute and prophylactic treatments. Here we discuss treatments with convincing evidence only.

Acute treatment of migraine attacks

The majority of people with migraine use non-prescription analgesics to treat acute migraine pain. Simple analgesics and NSAIDs can be effective in mild or moderate attacks[188]. Additional use of metoclopramide or another antiemetic can be recommended for those with nausea, although this recommendation is based on only limited evidence. Triptans are considered first-line treatment for moderate or severe attacks.

Triptans. Triptans are selective agonists at vascular 5-HT_{1B} and neuronal 5-HT_{1D} receptors and, for most, 5-HT_{1F} receptors[1]. Upon receptor binding, triptans cause 5-HT_{1B}-mediated vasoconstriction and, via 5-HT_{1D} and 5-HT_{1F} receptors, inhibit the release of CGRP, substance P, neurokinin A, glutamate and other vesicle-bound neuropeptides and neurotransmitters[77]. At the peripheral neurovascular junction, the inhibition of neuropeptide release from activated sensory trigeminal afferents prevents neurogenic vasodilation and inflammation in experimental animals, although solely blocking the latter mechanism is ineffective in acute migraine treatment[189]. In the central nervous system, presynaptic inhibition of neuropeptide release from first-order trigeminal neurons prevents activation and/or sensitization of central second-order neurons in the trigeminal nucleus caudalis[190].

Clinically, seven triptans are available, all of which are oral formulation: sumatriptan, almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan and zolmitriptan. Sumatriptan is also available as a suppository in some regions, and as subcutaneous and, like zolmitriptan, intranasal formulations. Most patients prefer tablets, although gastrointestinal absorption during migraine attacks is usually disturbed and highly variable owing to nausea and vomiting and gastrointestinal stasis; accordingly, oral doses are higher and are associated with slower onset of action, and lower, and interindividually and intraindividually (across attacks) more variable efficacy and tolerability. In fact, if oral triptans have failed, there is still a good chance that subcutaneous sumatriptan might be effective in subsequent attacks. The subcutaneous formulation is also more convenient for patients with severe ictal nausea and vomiting, and for those whose pain peaks rapidly (such as in early-morning migraine). The downside is the more frequent and more pronounced, although usually short-lasting, adverse events with the subcutaneous formulation. Oral triptans are pharmacokinetically more alike than different, with the exception of longer half-lives for frovatriptan and naratriptan[191,192]. Eletriptan has greater central penetration and is associated with more frequent central adverse events[77].

Subcutaneous sumatriptan[193] has the lowest number needed to treat for any triptan formulation (2.3 for 2 h pain-free), but all oral triptans have strong evidence for acute efficacy[191,194]. Eletriptan and rizatriptan have the highest 2 h pain-free and 24 h sustained pain-free rates[192]. The antimigraine effect of triptans might be too short in one-third of patients, resulting in recurrence of the migraine features within 24–48 h after an initial good response. Accordingly, patients should be instructed that recurrence might occur and that a repeat dose will usually be effective[193]. Although erroneously recommended in some labels, repeat dosing if the initial dose is ineffective does not afford additional benefit[193] and might lead to triptan overuse.

Of note, recurrence of headache within 24–48 h after an initial response to treatment is not restricted to triptans and can occur with all acute antiheadache medications, especially in long attacks, such as perimenstrual attacks. Of note, a drug associated with a low recurrence rate is only useful if the initial responder rate is at least similar to that of effective agents. Recurrence rates must, therefore, always be presented in conjunction with the initial responder rates. Eletriptan or frovatriptan might sometimes be helpful in patients with frequent recurrence. Combining the triptan with a long-acting NSAID might provide enhanced efficacy and reduce the risk of recurrence if the 2-h response is suboptimal[195]. Stepped care within an attack, by using a triptan only if an NSAID has failed, should be avoided as it is usually associated with reduced efficacy[196].

Patients in clinical trials are instructed to only take the study medication until the headache is moderate to severe, to enable a standardized assessment of whether patients improve from moderate or severe, to mild or no headache[197]. However, in clinical practice, most patients prefer treating a migraine as soon as possible. Indeed, treating as soon as possible should limit the patient's suffering, enhances efficacy and reduces recurrence risk[102]. However, formal clinical trial evidence in support of this approach is lacking[198]. As triptans may have reduced antimigraine efficacy when administered during aura[199] and are ineffective against aura, triptans might be best taken after aura, but as soon as possible after headache onset.

Acute adverse events associated with the use of triptans such as paraesthesia, flushing and palpitations are common but usually mild and brief (<15 min)[192]. Rarely, angina pectoris-like chest, neck and arm pressure, tightness and pain may occur, but are also usually brief and seldom severe. Although originally feared to be caused by coronary ischaemia owing to 5-HT_{1B} receptor-mediated vasoconstriction, this now seems extremely unlikely[200–202], and oesophagus or thoracic muscle spasms may be a better and much more reassuring explanation. Unlike ergot derivatives, triptans are remarkably safe, even in patients with comorbid cardiovascular disease, and are generally well tolerated[200–203]. Serious cardiovascular adverse events are rare[201,202]. Despite these reassuring observations, cardiovascular disease is a label contraindication owing to lack of formal safety data as such patients were excluded from the trials. Almotriptan or naratriptan are associated with the lowest incidence of adverse effects and may be reasonable choices for those who experience significant triptan-related adverse effects[192]. Prewarning patients regarding possible adverse events and that these effects are usually mild and transient might prevent panic and unnecessarily stopping the drug in future attacks. Rizatriptan, frovatriptan and zolmitriptan do not have a sulfonyl or a sulfonamide moiety and may be preferred in patients with sulfonamide allergy. Although it is probably best to avoid triptans during pregnancy, use of sumatriptan was not associated with increased risk of congenital defects[204].

Depression and anxiety are comorbid with migraine. Risk of serotonin syndrome in patients taking triptans and selective serotonin and noradrenaline reuptake inhibitors (SSRIs/SNRIs) has raised concern[205], but appears to be very low[205]. An exception may be patients overusing triptans. Although triptan overuse per se does not cause serotonin syndrome, in patients using SSRIs/SNRIs it may be less safe. Thus, patients treated with SSRIs/SNRIs can still use, but should not overuse, triptans.

Ergot derivatives. Ergot derivatives have been used extensively for more than half a century, but are now seldom used because of their unpredictable efficacy owing to poor oral bioavailability, their frequent association with severe nausea, and a high risk of overuse and, sometimes fatally, general vasoconstriction (ergotism)[206]. Parenteral dihydroergotamine is primarily used in the USA for inpatient management of patients who are intolerant or not responding to triptans, but scientific evidence supporting its use is poor.

Opioids and barbiturates. Although there is some evidence for limited efficacy of opioids and barbiturates in the treatment of migraine, guidelines strongly recommend against their use for this indication[188,207] because of the high risks of habituation, addiction, tolerance, withdrawal syndromes, adverse effects (sedation, dizziness and constipation), and medication overuse headache with these therapies.

Emerging acute therapies. Ubrogepant and rimegepant, small-molecule CGRP receptor antagonists (gepants), and lasmiditan, a selective 5-HT_{1F} receptor agonist (ditans) inhibiting trigeminocervical traffic, are emerging and recently approved acute antimigraine medications that, unlike triptans, lack vasoconstrictor activity[208–212] (Supplementary Table 1). As such, these treatments provide the proof-of-principle that, in contrast to previous belief, vasoconstriction is not required for antimigraine efficacy. Overall the efficacy of gepants[209,210] and lasmiditan[211,212] is, on a population basis, similar to or less than that of triptans, albeit with the caveat of comparing across studies. In contrast to triptans, gepants and lasmiditan have a potentially more favourable acute cardiovascular adverse effect profile. Trials are underway to study their potential in people who do not respond to triptans. Lasmiditan is associated with dizziness and vertigo, and, accordingly, there is a prohibition on driving motor vehicles or operating heavy machinery for at least 8 h after taking the medicine, and the potential for abuse. In experimental models, gepants seem less likely to induce medication overuse than triptans and ditans[213].

Emerging non-pharmacological therapies. Neuromodulation may be beneficial as adjunctive or monotherapy in patients who prefer non-pharmacological options or have experienced adverse events or lack of efficacy from medical therapy. External trigeminal nerve stimulation (adults only)[214–216] and, from 12 years of age, single-pulse transcranial magnetic stimulation (when administered during aura)[217] and non-invasive vagal nerve stimulation[218,219], possibly by inhibiting firing of

third-order sensory thalamocortical projections[220], SD and neuroinflammation[221], are approved for migraine attack prevention. Single-pulse transcranial magnetic stimulation (when administered during aura)[217], remote electrical neuromodulation (in those >12 years of age)[222], and non-invasive multichannel electrical stimulation of the trigeminal and occipital nerves are approved for the treatment of acute attacks, although published peer-reviewed data for multichannel electrical stimulation are not yet available.

Preventive medications for migraine attacks

Current preventive medication. Traditional migraine preventives are non-specific, initially intended for other indications, and consequently are often associated with poor and unpredictable effectiveness, tolerability and adherence[223] (BOX 5). No more than one-third of patients experience a truly successful response[223]. Troublesome adverse events are common, often necessitating early discontinuation, before a therapeutic dose is achieved. For many agents, the evidence is limited and comparative trials are lacking, essentially precluding evidence-based guidelines. Physicians' prescriptions are best described as 'trial and error' and largely based on individual and cultural preferences.

European guidelines[223] recommend a limited number of reasonably well-established preventives for patients with two or more disabling attacks per month, despite appropriate use of acute medications. By contrast, North American guidelines[224,225] recommend a more extensive list, which also includes several preventives with only limited evidence, for patients with four or more attacks or ≥8 days of migraine headache a month that substantially interfere with quality of life despite appropriate use of acute medications. Shared indications include patients who have failure of, contraindication to, overuse of, or troublesome side effects from acute medications, and patients with frequent, prolonged or uncomfortable aura symptoms. Prescriptions usually start at low doses with slow titration over weeks to months to a therapeutic dose or until intolerable adverse effects occur, and waiting for 2–3 months after the target dose is reached to assess efficacy or lack of it.

CGRP pathway monoclonal antibodies. Monoclonal antibodies (mAbs) that specifically target the CGRP peptide (eptinezumab, fremanezumab and galcanezumab) or canonical CGRP receptor (erenumab)[226] are approved for the preventive management of episodic and chronic migraine[227,228] (Supplementary Table 1). The site of antimigraine action is currently an area of major research effort[92]. Although a central action seems likely, the penetrance of mAbs into the brain seems very limited and probably subtherapeutic, with CSF levels 0.01% of plasma levels. Evidence is now accumulating that the trigeminal ganglion, an area of the brain that is not or less protected by the blood–brain barrier, allows mAbs to enter freely[92].

The efficacy of mAbs occurs within weeks and is sustained for years[227,228]. Short-term tolerability is very good to excellent, probably reflecting lack of active metabolites and off-target toxicity. Constipation and less frequently hypertension and anaphylaxis may occur, particularly with erenumab. The antibodies are target-selective and metabolized into amino acids and processed in the reticuloendothelial system rather than via the liver or kidneys[92]. However, long-term studies up to 5 years in duration have not raised major safety issues. Owing to the long half-life of mAbs, administration is only once every 1–3 months, with eptinezumab delivered intravenously and the others subcutaneously. Together with the good tolerability of these therapies, the dose regimen promotes adherence and persistence of use compared with other preventives that require twice or thrice daily dosing.

Comparing CGRP inhibitors with established preventives is methodologically challenging because the latter were tested decades ago, using partly different inclusion criteria, study populations, designs and end points. Overall, the therapeutic gains versus placebo seem similar, but the ≥50% responder rates (that is, the proportion of patients with ≥50% migraine reduction) seem higher with mAbs. Comparing all these therapies directly against each other is not feasible owing to the high number of trials that would be required. In a novel 'retention-type' trial, an approach similar to the approach that has been used extensively for anti-epileptics, the discontinuation rate due to adverse events with erenumab was substantially lower than that with topiramate, and the >50% responder rate was considerably higher[229].

In patients with high-frequency migraine, who had previously failed, were intolerant to, or had contraindications for two to four current preventives, erenumab[230], fremanezumab[231] and galcanezumab[232]

Box 5 | Current (established) migraine preventives[a] (REF.[273])

- Pizotifen
  - Weight gain
  - Drowsiness

β-Blockers

- Propranolol
  - Reduced energy
  - Tiredness
  - Postural symptoms
  - Contraindicated in those with asthma
- Metoprolol

Tricyclics

- Amitriptyline, dosulepin (dothiepin) and nortriptyline
  - Drowsiness
- Venlafaxine
  - Drowsiness
  - Urinary retention
  - Arrhythmias

Anticonvulsants

- Valproate
  - Drowsiness
  - Weight gain
  - Tremor
  - Hair loss
  - Fetal abnormalities
  - Haematological or liver abnormalities
- Topiramate
  - Paraesthesia
  - Cognitive dysfunction
  - Weight loss
  - Care with a family history of glaucoma
  - Nephrolithiasis
- Flunarizine
  - Drowsiness
  - Weight gain
  - Depression
  - Parkinsonism
- Botulinum toxin type A
  - Neck pain
  - Muscle weakness

Single studies

- Lisinopril, neutraceuticals riboflavin, coenzyme Q10, feverfew
  - Cough
  - Gastrointestinal upset
- No convincing evidence
  - Verapamil, gabapentin (studies shown to have been falsely reported)
- Controlled trials to demonstrate no effect
  - Nimodipine, clonidine, selective serotonin reuptake inhibitors: fluoxetine

[a]Common adverse effects are also listed.

showed superior efficacy to placebo. The therapeutic gains were all clinically relevant, suggesting that patients with high-frequency migraine who have failed treatment with multiple preventives may still benefit from treatment with these new biologics.

Gepants. Gepants (CGRP receptor antagonists) are effective for the acute treatment of migraine attacks, but also can prevent attacks when given daily, confirming that acute targets might also function as preventive targets. Treatment with atogepant taken once or twice daily over a 3-month period achieved >50% responder rates ranging from 52% to 62% compared with 40% for placebo[233]. Constipation and nausea were the most frequently reported adverse events, with discontinuation owing to adverse events occurring in ~3% of both the active treatment and placebo groups. Rimegepant taken every other day was also effective with a >50% responder rate of 49% compared with 41% for placebo[234]. Nausea was the most frequently reported adverse event and discontinuation owing to adverse events was slightly higher in the active treatment group (1.9%) than in the placebo group (1.1%).

Under normal circumstances, ischaemic events trigger compensatory local release of CGRP with resulting regional vasodilation and increased collateral flow to rescue the threatened tissue[235]. Consequently, concerns have been put forward that CGRP inhibitors might worsen the outcome of coincidental ischaemic events[235]. For cerebral ischaemia, this was indeed demonstrated in mice[236]. Cardiovascular safety of gepants and CGRP mAbs has been claimed following clinical safety studies[171,237,238], but important methodological criticism has been raised, including pharmacokinetic issues and that the studies were primarily conducted in men. Migraine is far more prevalent in women, in whom CGRP-mediated cardioprotective mechanisms are more important than they are in men[171,235,237–239]. Because of the high prevalence of migraine, extensive long-term post-marketing surveillance, particularly in patients with cardiovascular disease who are, therefore, at increased risk of ischaemic events, are needed. Follow-up studies, although reassuring[240], are still too limited in sample size and patient complexity to draw definitive conclusions. Moreover, patients with recent cardiovascular disease were excluded from these studies.

Behavioural therapies

Behavioural self-management, such as relaxation training, stress management, cognitive behavioural therapy and biofeedback, either alone, or in addition to drug therapy and/or aerobic exercise, may maximize outcomes and reduce disability in patients with migraine[241].

Chronic migraine with medication overuse

Many patients with chronic migraine overuse acute headache or migraine medication and/or caffeine-containing beverages. Usually, overuse leads to a cycle of daily repeated withdrawal headaches that are temporarily suppressed by repeated use of analgesics and/or caffeine. Individuals who manage to discontinue overuse permanently usually improve significantly, with a marked reduction of attack frequency and severity[242]. Acute and complete withdrawal seems logical and cost-effective[243,244], although withdrawal is often associated with severe withdrawal symptoms for several weeks, complicating perseverance. Owing to fear for these symptoms, many patients and physicians are hesitant to begin withdrawal.

Post-hoc analyses have suggested that topiramate[245] and onabotulinumtoxinA (BTA)[165] might sometimes be effective in treating chronic migraine with or without medication overuse even without withdrawal. However, the effect size is modest and confounded by unblinding owing to typical adverse events[244]. Whether patients should be managed by 'going cold turkey' (acute withdrawal and starting preventives only after 2–3 months, if necessary), by preventives plus tapering off overused medication, or by preventives without withdrawal is debated[242,243,245–247]. Comparing these strategies is challenging owing to blinding issues, varying inclusion criteria and difficulty in controlling for all possible medication combinations and dosages.

One study[244] assessed whether add-on therapy with BTA enhances the efficacy of acute withdrawal in a large randomized, double-blind, placebo-controlled, clinical trial. However, masked treatment with BTA did not afford any additional benefit over acute withdrawal alone, also not after repeated dosing. Withdrawal was effective and well tolerated. Explaining the rationale and motivation are crucial to the initiation of, perseverance with and success of withdrawal, but are often omitted because they are time-consuming. After successful withdrawal, restriction of acute medications and, if necessary, preventives are crucial to preventing a relapse.

Post-hoc subgroup analyses have suggested that CGRP mAbs[248,249] and BTA[247] might be effective without withdrawal instructions. Unblinding owing to adverse events does not seem to be an issue. Prospective controlled studies confirming these preliminary results and better delineating the effect size are awaited.

Overall, prevention of medication overuse headache by limiting the consumption of simple analgesics or NSAIDs to <12 days per month, and that of combination analgesics, opioids, ergots or triptans to <10 days per month, seems to be the best approach.

Hemiplegic migraine and prolonged aura

Controlled preventive trials for hemiplegic migraine are lacking owing to the rarity of this condition[140]. Treatment is empirical and based on only small case series. Flunarizine, acetazolamide, verapamil and anticonvulsants such as lamotrigine and divalproex sodium have all demonstrated some efficacy[138,140]. In a randomized controlled trial of 30 participants with migraine with prolonged aura, ketamine nasal spray reduced the severity but not duration of the aura[250]. Triptans do not affect SD, the likely mechanism for hemiplegia and other aura symptoms[15,139,151,153]. Consequently, triptans can be safely used for treating the headache of hemiplegic migraine, despite a contraindication in the label as no formal safety data for this population are available.

Quality of life

Experiencing a migraine attack is classified within the highest WHO disability class[9]. Moreover, the disease migraine is listed by The Global Burden of Disease Study as the third most disabling disease worldwide, expressed as years lived with a disability[236]. Migraine accounted for more than half of the 42.9 million years lived with disability of all neurological disorders. By also including medication overuse headache, migraine was even ranked second in terms of years lived with disability[4,251]. Migraine may also seriously affect life between attacks, owing to a lack of understanding and dismissal of the erratic paroxysmal nature of the disease, fear of the next attack and its likely inconvenient timing, resulting in repeatedly cancelling social and work appointments at the very last moment, and hindrance of career progression due to absence from work and poor performance during attacks and the pre-ictal and postictal phases.

Migraine, especially chronic migraine, also represents a major economic burden for society. In an estimation of the annual costs of brain disorders in the EU in 2010, migraine accounted for >18 billion euros in direct and indirect costs (mainly work loss)[252]. A more recent study by the European Work Foundation estimated a figure of 95 billion euros per year[253].

Outlook

Treatment pipeline

Although greatly improved over the past three decades, there is a clear need to further refine migraine management. The pipeline is relatively rich with potential new medicines and targets (Supplementary Table 1). Several issues are associated with current acute therapies: not all patients respond, not all attacks in any patient respond, relapse can occur after initial improvement, there are tolerability and safety issues, and there is a risk of overuse. Medicines that render patients pain-free in a timely fashion without headache recurrence, with good inter-attack consistency, little risk of overuse, and excellent tolerability and safety, are desired. Cardiovascular and cerebrovascular safety are key drivers to avoid the 5-HT_{1B} receptor-mediated vasoconstrictor effect of triptans, although triptans have proven to be safe in clinical practice, and vascular fears have largely faded. Indeed, emerging non-vasoconstrictor gepants and ditans are clinically effective.

Preventive treatments are in many ways more urgent a need as there is not a single migraine-bespoke and well-tolerated and effective oral preventive medicine used in clinical practice. Some studies have estimated that at least 40% of patients with episodic migraine, and in essence all patients with chronic migraine, need a preventive treatment. Proof of principle of CGRP pathway inhibitors as both preventive and acute treatments has been established, and they have just started to, or will soon, become available in clinical practice. PACAP mAbs are currently in development. Glutamate-based targets may work as well; however, important adverse effects need to be resolved. Neuromodulation strategies using implanted devices have thus far been disappointing, whereas non-invasive devices such as single-pulse transcranial magnetic stimulation[217], supraorbital nerve stimulation[215], and (partially) non-invasive vagal nerve stimulation[218] have been the subject of proof-of-principle studies and several have been approved. The additive effects of the various behavioural therapies are to be investigated as well.

Outstanding research questions

Despite major recent success in better understanding migraine pathophysiology, there are still a number of important questions that need to be addressed. Among these is identifying the true triggers for migraine attacks, the mechanism by which they precipitate attacks, and how personal they are. Moreover, identifying the primary event that initiates a migraine attack is required, in addition to identifying the processes that occur between administration of experimental triggers of migraine (such as nitric oxide and CGRP) and migraine onset, and the generation of pain perception. Furthermore, the mechanisms by which female sex hormonal fluctuations and other factors exacerbate or facilitate migraine attacks requires further study. Only about one-third of patients respond extremely well to CGRP mAbs and one-third do not respond at all. As such an all-or-nothing clinical effect for mAbs seems unlikely to be explained by inter-individual pharmacokinetic variability, there may be different types of migraine, some mainly CGRP-dependent and others mainly CGRP-independent. The mechanisms that account for the increased risk of cerebrovascular and cardiovascular events in individuals with migraine with aura, and the role of blood vessels in migraine pathophysiology, also require further study, as do the genetic signatures that predispose to migraine subtypes and their underlying mechanisms, including whether there is any involvement of epigenetic factors.

Regarding the treatment of migraine, one major outstanding question is the underlying mechanism and site of action of migraine therapies. Migraine attacks begin with central nervous system symptoms and correlate with changes in brain activity that can be visualized with functional imaging. Yet growing evidence indicates that effective migraine therapies such as dihydroergotamine, triptans and CGRP inhibitors primarily, if not exclusively, act outside the brain. Where and how triptans, dihydroergotamine and CGRP inhibitors work is still to be determined, as is the extent of brain access required for treatments to work. Moreover, whether SD is truly involved in the initiation of migraine attacks, even those that are not associated with aura, and whether blocking SD prevents migraine attacks with and without aura is unknown.

In addition, treatment is not effective in all patients with migraine and not all attacks in an individual respond, but the factors that predict efficacy and consistency are unknown. Identifying these factors — such as whether there are (possibly genetically determined) endophenotypes in migraine that can better predict treatment outcome or adverse effect profiles — could allow personalized medicine in the future. Safety concerns regarding some treatments for migraines also requires further study, including the cerebrovascular and cardiovascular safety of blocking CGRP-mediated (rescue) mechanisms in ischaemic events. Finally, whether medication overuse

headache is a distinctive complication of migraine rather than a secondary headache still needs to be determined, as does the best treatment protocol for medication overuse headache, whether it is detoxification or preventive migraine medication, or a (stepwise?) combination of the two. Finally, why migraine is so common and whether any developmental components are involved in its pathophysiology require further study.

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Author contributions

Introduction (M.D.F., D.W.D. and P.J.G.); Epidemiology (T.K. and M.D.F.); Pathophysiology (C.A., M.A., R.B., A.C., P.J.G., M.D.F. and A.M.J.M.v.d.M.); Diagnosis, screening and prevention (D.W.D. and M.D.F.); Management (D.W.D., P.J.G. and M.D.F.); Quality of Life (T.K.); Outlook (A.C., P.J.G., D.W.D. and M.D.F.); Overview of the Primer (all authors).

Competing interests

D.W.D. reports the following conflicts: consulting: AEON, Amgen, Clexio, Cerecin, Cooltech, Ctrl M, Allergan, Alder, Biohaven, GSK, Linpharma, Lundbeck, Promius, Eli Lilly, eNeura, Novartis, Impel, Satsuma, Theranica, WL Gore, Nocira, XoC, Zosano, Upjohn (Division of Pfizer), Pieris, Praxis, Revance, Equinox; honoraria: Clinical Care Solutions, CME Outfitters, Curry Rockefeller Group, DeepBench, Global Access Meetings, KLJ Associates, Academy for Continued Healthcare Learning, Majallin LLC, Medlogix Communications, MJH Lifesciences, Miller Medical Communications, Southern Headache Society (MAHEC), WebMD Health/Medscape, Wolters Kluwer, Oxford University Press, Cambridge University Press; research support: Department of Defense, National Institutes of Health, Henry Jackson Foundation, Sperling Foundation, American Migraine Foundation, Patient Centered Outcomes Research Institute (PCORI); stock options/shareholder/patents/boards of directors: Ctrl M (options), Aural Analytics (options), ExSano (options), Palion (options), Healint (options), Theranica (options), Second Opinion/Mobile Health (options), Epien (options/Board), Nocira (options), Matterhorn (shares/Board), Ontologics (shares/Board), King-Devick Technologies (options/Board), Precon Health (options/Board); patent 17189376.1-1466:v (title: Botulinum Toxin Dosage Regimen for Chronic Migraine Prophylaxis). M.A. is a consultant or scientific advisor for AbbVie, Allergan, Amgen, Eli Lilly, Lundbeck, Novartis and Teva; a primary investigator for ongoing Amgen, AbbVie/Allergan and Lundbeck trials; and has received grants from Lundbeck Foundation, Novo Nordisk Foundation and a research grant from Novartis. T.K. reports having contributed to an advisory board of CoLucid and a research project funded by Amgen, for which the Charité—Universitätsmedizin Berlin received an unrestricted compensation; he further reports having received honoraria from Lilly, Newsenselab, and Total for providing methodological advice, from Novartis and from Daiichi Sankyo for providing a lecture on neuroepidemiology and research methods, and from the BMJ for editorial services. P.J.G. reports, over the last 36 months, grants and personal fees from Amgen and Eli-Lilly and Company, a grant from Celgene, and personal fees from Alder Biopharmaceuticals, Aeon Biopharma, Allergan, Biohaven Pharmaceuticals Inc., Clexio, Electrocore LLC, eNeura, Epalex, GlaxoSmithKline, Impel Neuropharma, Lundbeck, MundiPharma, Novartis, Pfizer, Praxis, Sanofi, Santara Therapeutics, Satsuma, Teva Pharmaceuticals, Trigemina Inc., WL Gore, and personal fees for advice through Gerson Lehrman Group, and Guidepoint, fees for educational materials from Massachusetts Medical Society, Medery, Medlink, PrimeEd, UptoDate, WebMD, and publishing royalties from Oxford University Press, and Wolters Kluwer, and for medicolegal advice in headache, and a patent magnetic stimulation for headache (no. WO2016090333 A1) assigned to eNeura without fee. M.D.F. reports grants and consultancy or industry support from Electrocore, Medtronic, Eli Lilly, Amgen, Novartis, Satsuma, Lundbeck, and TEVA, and independent support from The Netherlands Organisation for Scientific Research (NWO), The Netherlands Organisation for Health Research and Development (ZonMW), The Dutch Brain Foundation, The Dutch Heart Foundation, The Dutch Ministry of Health, and The NutsOhra Foundation from the Dutch Insurance Companies. A.C. is a compensated consultant for Amgen, Biohaven, Eli Lilly, Lundbeck, and Satsuma; he is on the executive board of the American Headache Society. R.B. is the John Hedley-Whyte Professor of Anaesthesia and Neuroscience at the Beth Israel Deaconess Medical Center and Harvard Medical School; he has received research support from the NIH (R01 NS094198-01A1, R37 NS079678, R01NS095655, R01 NS104296, R21 NS106345), Allergan, Teva, Dr. Ready, Eli Lilly, Trigemina and the Migraine Research Foundation; he is a reviewer for NINDS; he holds stock options in AllayLamp, Theranica and Percept; he serves as consultant, advisory board member, or has received honoraria from: Alder, Allergan, Amgen, Autonomic Technologies, Avanir, Biohaven, Dr. Reddy's Laboratory, electroCore, Eli Lilly, GlaxoSmithKline, Merck, Pernix, Theranica, Teva, and Trigemina; and has received CME fees from Healthlogix, Medlogix, WebMD/Medscape. A.M.J.M.v.d.M. reports grants and or industry support from Precision Medicine and Schedule 1 Therapeutics and independent support from The Netherlands Organisation for Scientific Research (NWO) and The Netherlands Organisation for Health Research and Development (ZonMW). C.A. declares no competing interests.

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